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# Novel Antimalarial Drug Screening Based on Methyl Eugenol, Cinnamaldehyde, and Thiosemicarbazone with Cysteine Protease Inhibition: In Silico Molecular Docking, Molecular Dynamics, and ADMET Studies

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## ABSTRACT

*Plasmodium falciparum* malaria contributes to significant global diseases. Computer-aided drug design, screening, and discovery were used to analyze a novel series of Methyl Eugenol Benzaldehyde Thiosemicarbazone (MEBThi) and Methyl Eugenol Cinnamaldehyde Thiosemicarbazone (MECThi) derivatives for malaria *falciparum* inhibition. This present study showed that 16 molecules from 28 of MEBThi and MECThi have affinities and interaction with active-site residues of cysteine protease, a key player in erythrocyte proliferation of *P. falciparum.* 13-MECThi demonstrates the best binding affinity at -8.0 kcal/mol while co-drug -5.6 kcal/mol. Physicochemical and pharmacokinetic assays of 13-MECThi have also revealed this potent compound. Toxicity analysis shows that 13-MECThi does not have mutagenicity and carcinogenicity characters, whereas co-drug has mutagenicity probability. The molecular dynamic evaluation illustrated that the 13-MECThi complex has higher Root Mean Square Deviation (RMSD) values, indicating its structure was more flexible than the chloroquine complex. Root Mean Square Fluctuation (RMSF) complex of receptor and 13-MECThi has no fundamental differences with chloroquine complex. This designed compound should be considered a *falciparum* antimalarial drug.

Keywords: methyl eugenol, cinnamaldehyde, thiosemicarbazone, *Plasmodium falciparum*

## INTRODUCTION

*Plasmodium falciparum* infection in malaria has enormous implications in damaging erythrocytes [1], [2], extending to multiple organ complications [3], [4], and mortality [5], [6]. This disease was further exacerbated by the incidence of drug resistance [7], [8] and a long time of recovery treatment [9], [10]. All of these reasons make the need to develop novel antimalarial drugs urgent.

Drug discovery should focus on regenerated raw materials and the active functional group. Eugenol, methyl eugenol, and cinnamaldehyde are natural compounds abundant in essential oils (EO) plants. Eugenol is a significant component in *Syzygium aromaticum*, *Ocimum basilicum*, *Glycine max (L.) Merr.*, *Croton zehntneri Pax et Hoffm*, and *Laurus nobilis L.* [11], [12]. Eugenol can be converted into methyl eugenol. Natural methyl eugenol was a phenylpropanoid derived from eugenol found in more than 400 species [13], [14], such as *Agastache Mexicana ssp*. [15] *Piper cubeba L.* [16] and, *Pimenta pseudocaryophyllus* [17].

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Meanwhile, natural cinnamaldehyde could be extracted from essential oil plants such as *Cinnamomum cassia* and *C. verum* [18]. Methyl eugenol (ME) and cinnamaldehyde were reported to have broad-spectrum activity [19], [20]. The ME and cinnamaldehyde potencies as renewable materials and their broad bioactivities encourage the exploration of these two materials as antimalarials.

Thiosemicarbazone or aminothiourea functional group is a molecule with an imine group on the aryl or alkyl group. The thiosemicarbazone molecule donates a C=N-NH-CS-NH [21], [22], and several side groups (R/Ar) positions that can be designed. Thiosemicarbazone compounds were reported as the active group with antimicrobial [23], [24], and antiprotozoal potencies [25], [26].

The mixture design approach to develop phytoformulations was generally carried out to optimize the potential of major compounds in essential oil-producing plants. The efficacy of acaricide on the cow lice *Rhipicephalus (Boophilus)* microplus reached 100% in a combination of *Cinnamomum zeylanicum* (2/3): *Cumin cyminum* (1/6) and *Pimenta dioica* (1/6), with the main components being methyl eugenol and cinnamaldehyde [27]. However, methyl eugenol was assumed to be genotoxic [28]. Methyl eugenol active site conversion needs to be done to minimize this character.

The thiosemicarbazone side groups with methyl eugenol and cinnamaldehyde form Methyl Eugenol Benzaldehyde Thiosemicarbazone (MEBThi) and Methyl Eugenol Cinnamaldehyde Thiosemicarbazone (MECThi) for *falciparum* antimalarial purposes and its toxicities studies was undetermined.

This study evaluates MEBThi and MECThi derivates for *falciparum* antimalarial by in silico (molecular docking and molecular dynamics) and observes their chemoinformatics profile.

## EXPERIMENT

### Materials

A series of MEBThi and MECThi were used as tested compounds (Figure 1). Chloroquine (C) 3D structure was retrieved at http://www.chemspider.com/2618 and used as a co-drug. The three-dimensional macromolecule of cysteine protease was obtained from the RCSB protein databank by 1YVB of PDB ID.

### Protein and ligand preparation

The MEBThi and MECThi derivatives structure were made by Marvinsketch. All molecules were structure prepared into ligands by adding hydrogen and AMBER ff 14SB - Gasteiger charges. The 1YVB chain A was used as a receptor. Water and native ligand in the receptor were eliminated by using Chimera 1.13.1. Optimization of the receptor was conducted by adding hydrogen and charged by AM1-bcc.

### Molecular docking

The screening was carried out with the open-source software of PyRx version 0.8 [29]. Redocking was done. Virtual screenings were applied five times to produce affinity energy accurately. Docking results and interaction patterns between ligands and receptors were visualized using the Discovery Studio Visualizer 2019 Client. The grid box was determined at center X = 84.1018; Y = - 36.1837; Z = - 89.6053; dimension (Å) at 23.1341, 25.0000, and 25.0000 in x, y, z, consecutively.



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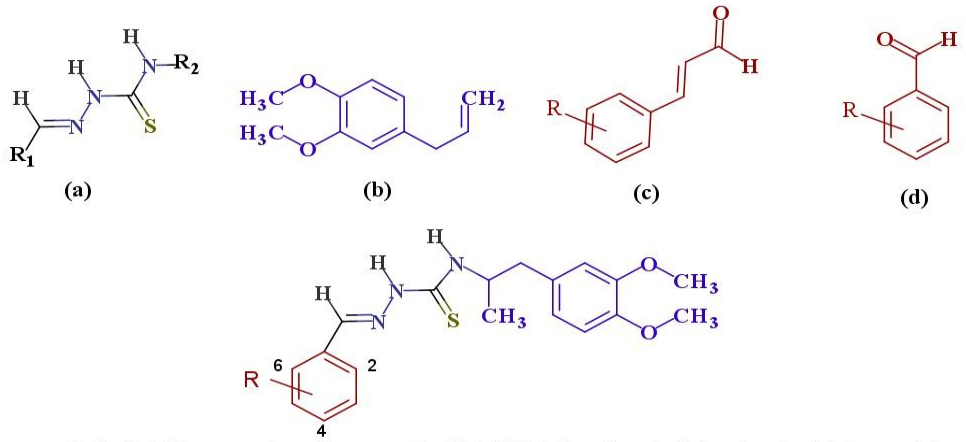
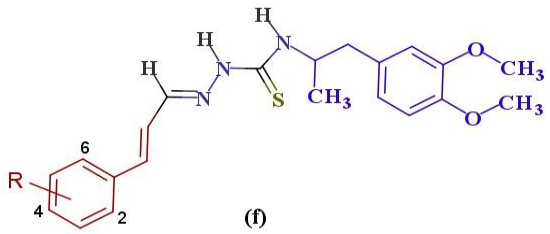
**Physicochemical, pharmacokinetics, and bioactivities of compound**

SwissADME was selected for physicochemical and pharmacokinetics evaluator. Bioactivities and toxicity tests of ligands were carried out respectively by Molinspiration and Lazar [30].




1-MEBThi/1-MECThi, R = H
2-MEBThi/2-MECThi, R = 2 - $NO_2$
3-MEBThi/3-MECThi, R = 3 - $NO_2$
4-MEBThi/4-MECThi, R = 4 - $NO_2$
5-MEBThi/5-MECThi, R = 2 - Cl
6-MEBThi/6-MECThi, R = 3 - Cl
7-MEBThi/7-MECThi, R = 4 - Cl
8-MEBThi/8-MECThi, R = 4 - $CH_3$
9-MEBThi/9-MECThi, R = 4 - $OCH_3$
10-EBThi/10-MECThi, R = 4 $N(CH_3)_2$
11-MEBThi/11-MECThi, R = 2 - OH
12-MEBThi/12-MECThi, R = 3 - OH
13-MEBThi/13-MECThi, R = 4 - OH
14-MEBThi/14-MECThi, R = 3 - $OCH_3$
4 - OH

(g)

**Figure 1.** The structure of (a) thiosemicarbazone, (b) methyl eugenol, (c) cinnamaldehyde, (d) benzaldehyde, (e) methyl eugenol benzaldehyde thiosemicarbazone derivate, (f) methyl eugenol cinnamaldehyde thiosemicarbazone derivate, (g) substituent variation

**Molecular dynamic**

The structural dynamic was simulated using YASARA software (version 19.14.12) [31]. Amber ff14sb force field [32] was applied under the following conditions: temperature 298 °K, 1 Barr pressure, pH 7.4, 0.9% NaCl concentration, 0.997 water density, and 20 ns simulation time.

## RESULT AND DISCUSSION

**Molecular docking analysis**

The molecular docking test was done to learn the interaction between the thiosemicarbazone ligand and the target receptor. Docking analysis showed that only 8 (eight) molecules of MEBThi and 8 (eight) molecules of MECThi derivates have affinities values (at



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RMSD 0.0) lower than the chloroquine and also bonded in the receptor active sites (Figure 2). This active site consists of free cysteine (Cys-25) and histidine (His-159). 13-MECThi has the lowest affinity energy value at -8.0 kcal/mol and -5.6 kcal/mol for chloroquine (molecule 15). Chloroquine is a commercial malaria drug that inhibits cysteine protease activity [33]. Cysteine protease has a key role in parasite life and growth. Plasmepsins, falcipains, and aminopeptidases rule hemoglobin degradation. These parts take effect for the antimalarial drug target [34]. Falcipains (cysteine protease) is an enzyme responsible for the proliferation of protozoa [35]. It has a comprehensive function and inhibitory effect as an antiplasmodial malaria receptor [36], [37]. It has several active sites on the enzyme surface layer [38].

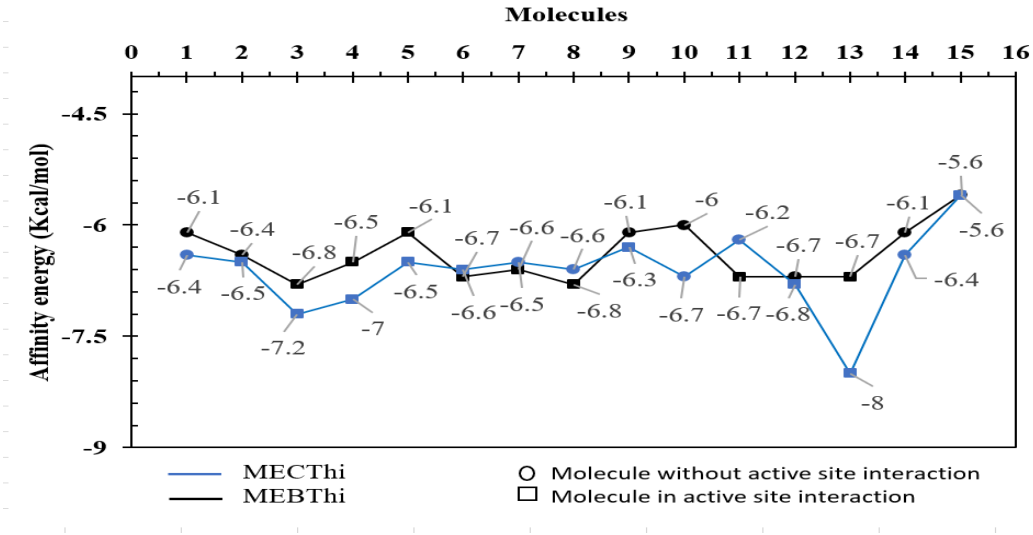


**Figure 2.** Graphical representation of binding affinities for 28 molecules and chloroquine

Docking analysis shows only 8 (eight) MEBThi derivates that have binding with the active site, namely 3-MEBThi; 4-MEBThi; 6-MEBThi; 7-MEBThi; 8-MEBThi; 11-MEBThi; 12-MEBThi; 13-MEBThi. Eight (8) MECThi derivates have interaction patterns with Cys-25 and His-159, including 2-MECThi; 3-MECThi; 4-MECThi; 5-MECThi; 6-MECThi; 9-MECThi; 12-MECThi; and 13-MECThi. All these sixteenth ligands have energy lower than co-drug. Affinities energy of all compounds was given in Figure 2, where a molecule with active site interaction was symbolized in a square box sign. The affinity value of MECThi was observed almost all the better than MEBThi. It was predicted to be influenced by a cinnamaldehyde conjugated double bond to the thiosemicarbazone's nitrogen (Figure 3). The binding orientation of chloroquine and 13-MECThi was compared and laid on the cysteine protease model's surface, as presented in Figure 4. Molecular docking and chemoinformatics studies on methyl eugenol and cinnamaldehyde derivatives containing nitrogen and sulfur groups were showed these two compounds derivatives were potential candidates for *falciparum* antimalarial drugs in terms of the compound containing substituents in the para position [39]. This assumption was positively correlated with the high energy affinity of 13-MECThi, which has a para position binding substitute pattern to both methyl eugenol and cinnamaldehyde.

The cysteine protease inhibition was influenced by the bond of hydrogen, Van der Waals, and π interactions between thiosemicarbazone and active site residue. 13-MECThi and active site receptor was patterned by Pi-sulfur bonding between sulfur-thiosemicarbazone and hydrogen-histidine via Van der Waals interaction (Figure 5). This interaction probably



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contributes to a higher affinity score of 13-MECThi than co-drug. However, there was a hydrogen bond on the chloroquine, not on the receptor active site.

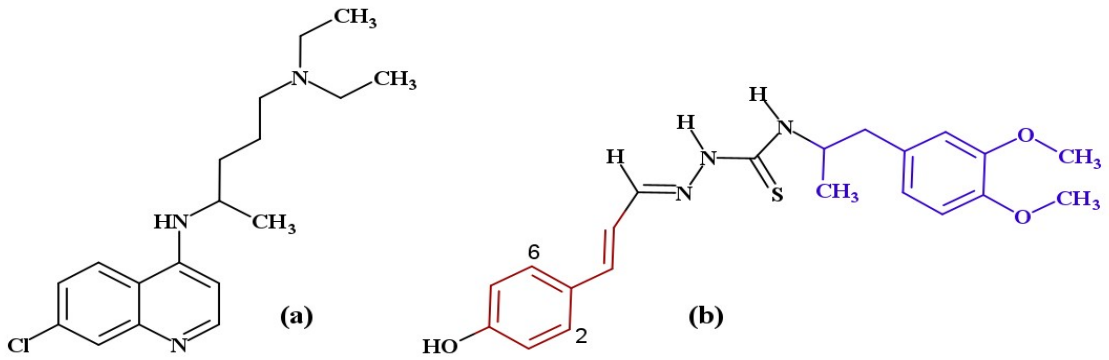


**Figure 3.** Structure of (a) chloroquine, (b) 13-MECThi

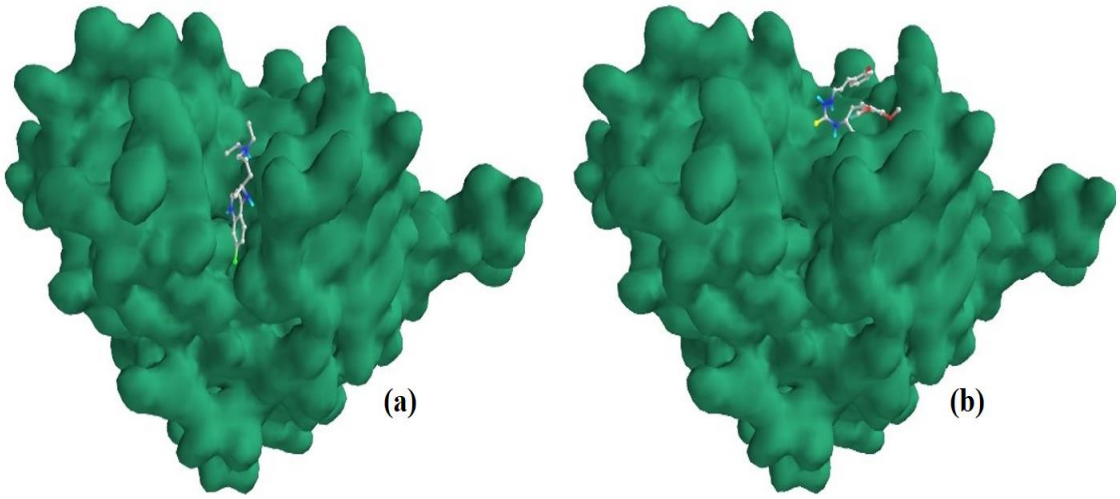


**Figure 4.** The complex interaction between 1YVB chain A with (a) chloroquine, (b) 13-MECThi

**Physicochemical, pharmacokinetics, and bioactivities analyses**

Drug-likeness was personalized by six physicochemical aspects: lipophilicity, flexibility, saturation, solubility, polarity, and molecule size. Bioavailability radar was visualized for chloroquine and 13-MECThi drug-likeness appraisal. Bioavailability radar consists of the compound lipophilicity (XLog P3) ranging from -0.7 to +5.0. Flexibility molecule no more than nine rotatable bonds. Saturation (Carbon fraction in the $SP^3$ hybridization) between 0.25 until 1.0. Solubility (LogS ESOL) from 0.0 to 6.0. Polarity (Topological Polar Surface Area) ranges from 20 $Å^2$ to 130 $Å^2$. Molecule size (MW) between 150 and 500 g/mol [40]. The testing molecule has to fall entirely in the dotted red line of the radar area to be considered drug-like. Figures 6a and 6b evaluate chloroquine and 13-MECThi (represented in blue lines) as predicted orally bioavailable. However, 13-MECThi was on the borderline of flexibility. It was probably influenced by the rotatable bonds of 13-MECThi of more than nine pieces [40].



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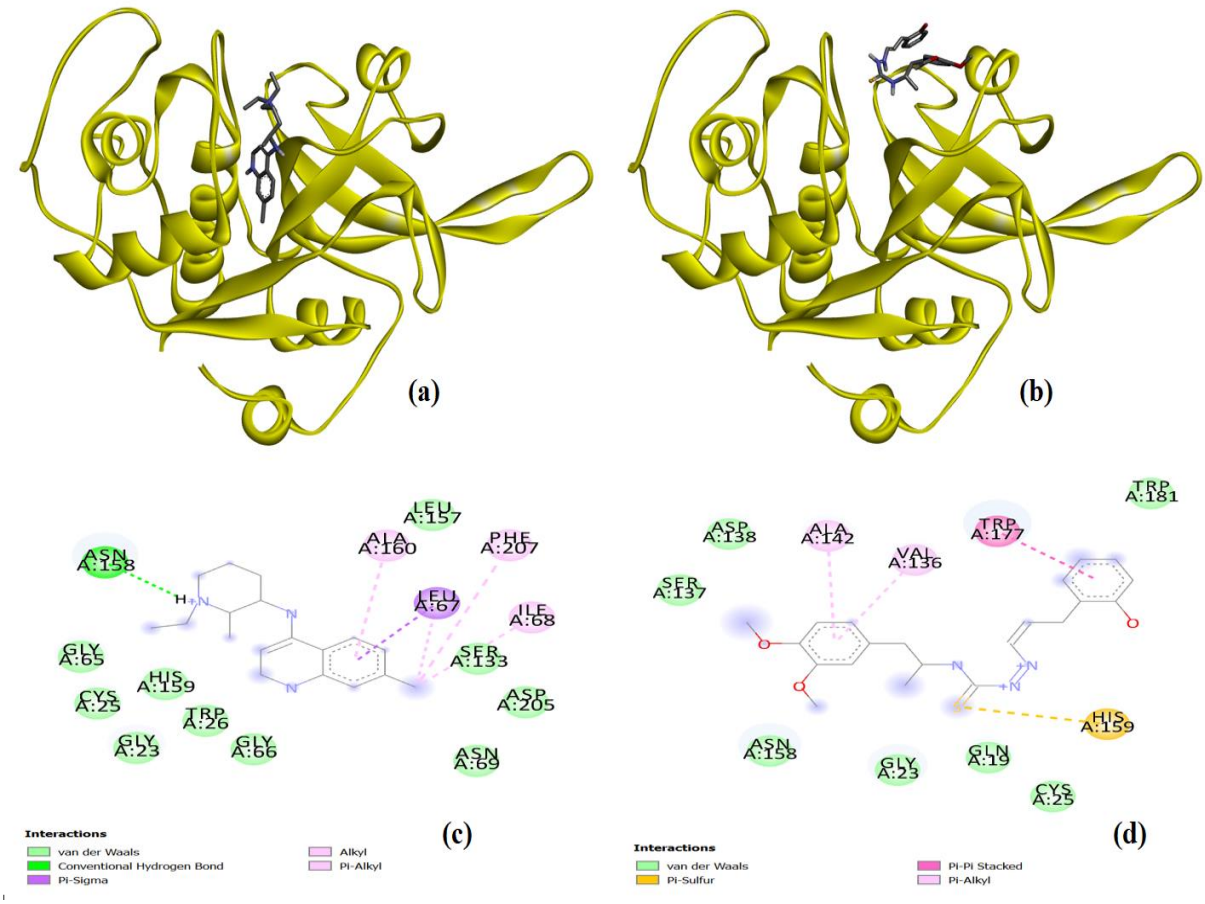


**Figure 5.** The binding poses and interacting residues of chloroquine (a, c) and 13-MECThi (b, d) with the cysteine protease

**Table 1.** Drug-likeness prediction

| Ligand | Rule of Lipinski* | | | | Rule of Veber** | |
|---|---|---|---|---|---|---|
| | MW | HBA | HBD | LogP | RB | TPSA |
| Chloroquine | 319.88 | 2 | 1 | 3.95 | 8 | 28.16 |
| 13-MECThi | 399.51 | 4 | 3 | 3.57 | 10 | 107.20 |
| *Lipinski rule: | MW: Molecular weight ≤ 500g/mol, HBA: Hydrogen Bond Acceptors ≤ 10, HBD: hydrogen bond donors ≤ 5, LogP ≤ 5 | | | | | |
| **Veber rule: | RB: Rotatable Bonds ≤ 9, TPSA 20 - 130 [40]. | | | | | |

The Boiled-Egg or Egan's Egg model predicted passive gastrointestinal absorption and active diffusion of drug molecules in the blood-brain. The egg white illustrates the physicochemical character that could be absorbed by the digestive tract (intestine). The yolk part shows the physicochemical space with a brain permeation probability [41]. Analysis of chloroquine and 13-MECThi shows that the drug malaria standard has a well-brain penetrant character distributed in egg yolk and 13-MECThi in the egg white, then assumed will be absorbed by the gastrointestinal tract (Figure 7).

Drug-likeness of a molecule was also described as Lipinksi and Veber rules (Table 1). The amount of rotatable bonds (RB) illustrates the freedom degree of ligand that influences its



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stability, re-arrangement conformation, and passive membrane transport. This descriptor must be less than or equal to 10 [42], [43]. Drug-likeness and toxicities of drug candidates were covered by pharmacokinetics. Drug candidate bioactivity was determined by the score of G-Protein-Coupled Receptor (GPCR) ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, and enzyme inhibitor. 13-MECThi was observed to be relatively active. Bioactivity scores of 13-MECThi and chloroquine were -2.99 and 0.99, consecutively. The higher the score, the greater the bioactivity prediction. A ligand's biological activity score ranges from - 5.0 to 0.0 was recognized as a ligand with medium activity, and more than 0.0 is intensely active. An inactive molecule has a score of less than -5.0 [44]. Bioactivities prediction of chloroquine and 13-MECThi was displayed in Figure 8.

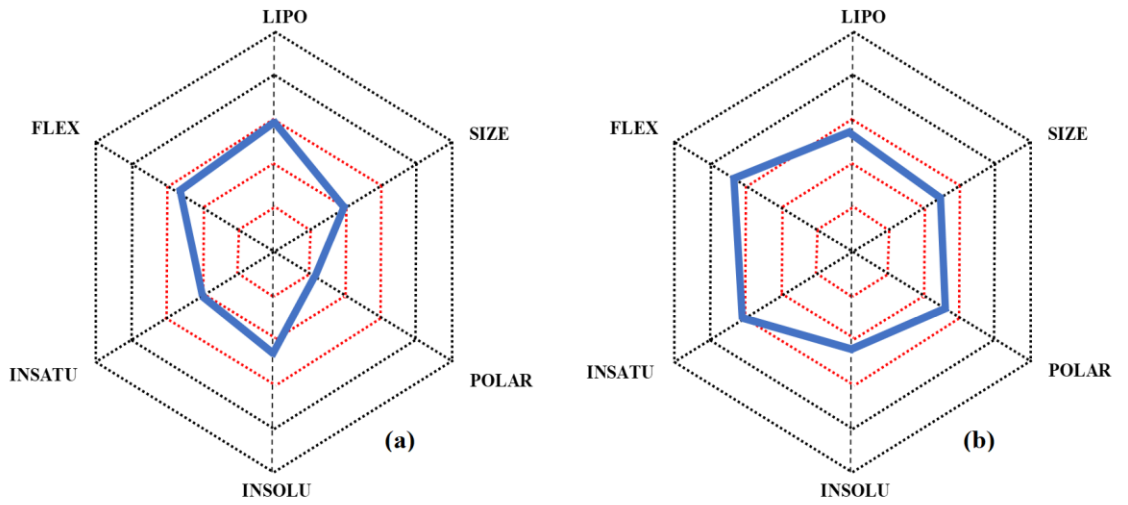


**Figure 6.** The bioavailability radar of (a) chloroquine, (b) 13-MECThi

A further assay using toxicity predictor pointed out that 13-MECThi was the potential malaria drug candidate since it has non-carcinogenic and non-mutagenic character (Table 2), and chloroquine has mutagenic properties.

Molecular dynamics (MD) is a valuable predictor of determining the macromolecules and ligand interaction at a certain time. The observed interactions can be in the form of conformational changes, protein folding, ligand binding, and others. These interactions will produce a receptor response, for instance, mutation, phosphorylation, protonation, removal, or addition of ligands [45]. Binding energy and stability obtained through MD are low-cost alternative assays for screening many drug candidates before being applied experimentally [45]–[47].

The parameter to determine the stability of the receptor and ligand complex during the MD process was named RMSD or Root Mean Square Deviation [48], [49]. Figure 9a describes a dynamic transition of the 1YVB chain A and 13-MECThi complex bonds at the beginning of the simulation (between 0 - 2 ns). It has also appeared at the end observation time between 13 – 20 ns. Meanwhile, in the 2 ns to 12.5 ns range, the 13-MECThi receptor complex tends to be as stable as the co-drug receptor complex. Overall, figure 9a illustrates that the 13-MECThi complex is more flexible than chloroquine in the test time range. It also figured out the stability of chloroquine and 13-MECThi according to the RMSD of ligand conformation during the simulation. As previously observed, there was a correlation between the flexibility of 13-



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MECThi (in radar bioavailability) and RMSD (in MD). These two parameters mutually support the prediction that 13-MECThi was more flexible than co-drug. Further experiments in a more extended period and higher temperatures are worth recommending before proceeding to the wet laboratory.

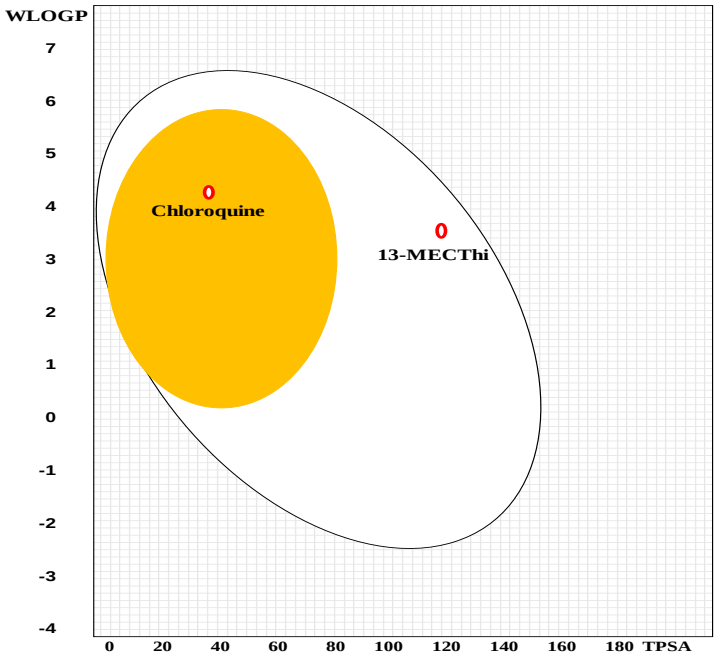


**Figure 7.** The boiled-egg of (a) chloroquine, (b) 13-MECThi

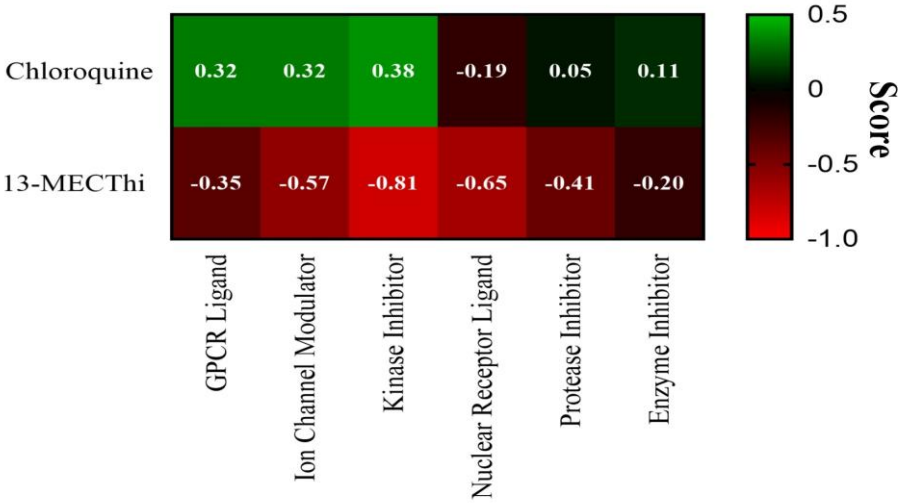


**Figure 8.** The bioactivity of (a) chloroquine, (b) 13-MECThi



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**Table 2.** Toxicity evaluation

| Molecule | Lazar prediction | |
|---|---|---|
| | Mutagenicity (Salmonella typhimurium) | Carcinogenicity (Mouse) |
| Chloroquine | M | Not find similar substances |
| 13-MECThi | NM | NC |

* M = Mutagenic; NM = Non-Mutagenic; C = Carcinogen; NC = Non Carcinogenic.

**Molecular dynamics analysis**

RMSF (Root-mean-square fluctuation) is a thermal flexibility parameter of the receptor and ligand complex. Relative fluctuations in RMSF were observed in the respective amino acids of the receptor and ligand during the simulation process [48], [49]. Figure 9b addresses that at 298 °K, 1 Barr pressure, pH 7.4, 0.9% NaCl concentration, and 0.997 water density, the movement of amino acid receptors tends to be stable, and there was no fluctuation starting from the beginning of 1 ns to 20 ns simulation time. Figure 9b was also described the influence of both ligands binding on the fluctuation of each residue of the cysteine protease according to the RMSF value during the simulation.

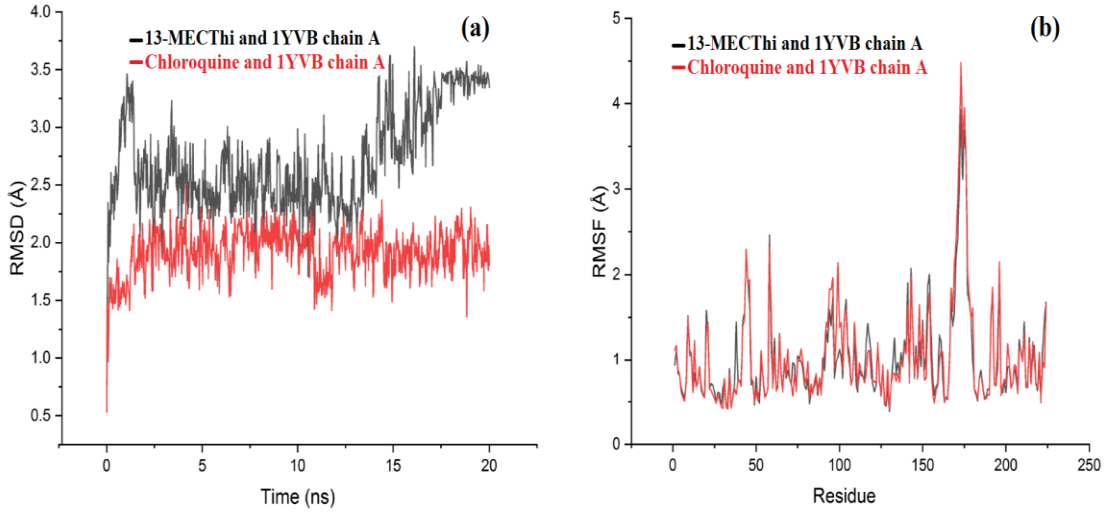


**Figure 9.** The chloroquine and 13-MECThi of (a) RMSD and (b) RMSF

## CONCLUSION

This precious basic research was malaria drug discovery with key compounds methyl eugenol and cinnamaldehyde, with thiosemicarbazone as the leading functional group. The 13-MECThi molecule is a promising drug candidate for treating *Plasmodium falciparum* malaria. For synthesis and in vitro assays, replacing para-hydroxy in cinnamaldehyde with other substituents was highly recommended to reduce flexibility, minimize rotatable bond, obtain more stable MECThi derivatives, and have better bioactivity than co-drug.

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